PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 92074.140204	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/043660	International filing date *(day/month/year)* 27 December 2004 (27.12.2004)	Priority date *(day/month/year)* 30 December 2003 (30.12.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NAGASAWA, Herbert, T.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 03 July 2006 (03.07.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/043660	27.12.2004	30.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/06, A61P43/00

Applicant
NAGASAWA, Herbert T.

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2004/043660

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-19,40-45,52-56, 63-66,72-75,81-84,90-93,96-104 and partially for claims: 1-10, 20-39,46-51,58-62,67-71,76-80,85-89,94,95 (see separate sheet); as well as claims 1-10,20-39,46-51,57 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 1-10,20-39,46-51,57 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 11-19,40-45,52-56, 63-66,72-75,81-84,90-93,96-104 and partially for claims: 1-10, 20-39,46-51,58-62,67-71,76-80,85-89,94,95 (see separate sheet)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-10,20-32,33-39 (partially), 46-51,57-62,67-71,76-80,85-89,94,95

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10,20-39,46-51,57,94,95
	No: Claims	58-62,67-71,76-80,85-89
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10,20-39, 46-51,57-62,67-71,76-80,85-89,94,95
Industrial applicability (IA)	Yes: Claims	58-62,67-71,76-80,85-89,94,95
	No: Claims	1-10,20-39,46-51,57 (see separate sheet)

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion

1. Claims 1-10,20-39,46-51,57 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Claims 1-10, 20-39,46-51,58-62,67-71,76-80,85-89,94,95 relate to a compound defined by reference to a desirable characteristic or property, namely "sulfhydryl protected glutathione prodrug", "..derivative thereof", " means for the determination of the ..",. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, the pathological condition(s) to be treated is/are functionally defined (... for reducing oxidative stress in a cell..", "..wherein reducing oxidative stress reduces...", "genetic disease", "physical injury", "..exposure to..") by a mechanism of action which does not allow to determine the diseases for which protection might legitimately be sought. Therefore, the claims cover a rather large number of diseases whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such diseases. Thus, the claims lack support and the application lacks disclosure (Article 5 PCT). Independent of the above reasoning, the claims also lack clarity (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of the compounds as disclosed in Figure 2 of the present application for the therapy of diseases

clearly specified in the claims or description (eg. claims 5,6,46); and with due respect to the general idea of the invention.

No opinion will be given in respect of subject matter which is not covered by the search report (Rule 66.1(e)PCT)

Re Item IV.

This Authority considers that there are two separate inventions covered by the claims indicated as follows:

1. Claims 1-10,20-32, 46-51,57-62,67-71,76-80,85-89,94,95 and partially 33-39:
A pharmaceutical composition comprising a sulfhydryl protected glutathione prodrug or the use of a sulfhydryl protected glutathione prodrug for the treatment of diseases associated with oxidative stress in a cell, in particular in drug induced hepatoxicity.

2. Claims 11-19, 40-45,52-56,63-66,72-75,81-84,90-93,96-104 and partially 33-39:
A pharmaceutical composition comprising a sulfhydryl protected cysteine prodrug (CySSMA) and/or the use of a sulfhydryl protected cysteine prodrug (CySSMA) for the treatment of diseases associated with oxidative stress in a cell, in particular in drug induced hepatoxicity.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem to be solved by the present invention is provision of a medicament for the treatment of diseases associated with oxidative stress in a cell, in particular drug induced hepatoxicity.

The solution proposed is the use of a sulfhydryl protected glutathione prodrug or a sulfhydryl protected cysteine prodrug (CySSMA).

Thiol group containing antioxidant prodrugs wherein the sulfhydryl group is protected represents the technical features which may , a priori, unify the subjects mentioned above.

The use of sulfhydryl protected cysteine prodrug (CySSMA) was known in therapy (see XP008051946 (Purdie J. W. (1970) Can. J. Chem. 49:725-730)). Moreover other sulfhydryl protected cysteine prodrugs such as L-CySSMĖ acid are known compounds already used in therapy of diseases associated with oxidative stress in a cell, in particular in drug induced hepatoxicity (see XP008051903 (Nagasawa et al. (1996) J. of Biochem. Toxicol 11(6):289-295)).

Consequently, the idea to use antioxidant prodrugs wherein the sulfhydryl group is protected in medicine is known in the state of the art and cannot serve as a single general inventive concept linking the subjects 1 and 2 which have no special technical features in common.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Therefore an opinion is given on the first subject mentioned (claims 1-10,20-32, 46-51,57-62,67-71,76-80,85-89,94,95 and partially 33-39).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this communication:

D1: US-a-5 382 679
D2: WO 02/090314 a
D3: US-B1-6 197 749
D4: XP002343366

D5: XP002343367
D6: WO 98/29375 a
D7: EP-a-0 494 405
D8: WO 01/80832 a
D9: WO 02/17962 a
D10: US-B1-6 369 106
D11: US-a-5 824 693
D12: EP-a-0 572 110
D13: EP-a-0 501 641
D14: US-B1-6 586 404
D15: XP008051903

1 NOVELTY (Art. 33(2) PCT)

1.1 The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 58-62,67-71,76-80,85-89 is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT):

1. Documents D1-D5 disclose a pharmaceutical composition comprising a sulfhydryl protected glutathione prodrug. Document D4 discloses the prodrug L-CySSG (see passages cited in the search report). Moreover the glutathione prodrugs GSSMA, GSSME, S-Ac-GSH-OEt were disclosed in the prior art (see figure 2 of the present application).

The applicant's attention is drawn to the fact that the features "..for reducing oxidative stress in a cell", "..for increasing glutathione levels in a cell", or "..for reducing hepatoxicity.." are of no relevance as far as the composition per se is concerned.

Therefore, the subject matter of claims 58-62,67-71,76-80,85-89 is not new (Article 33(2) PCT).

2 INVENTIVE STEP (Art. 33(3) PCT)

2.1 Even if novelty could be established for claims 58-62,67-71,76-80,85-89 the

subject matter of the present application would not meet the requirements of Art. 33(3) PCT. Sulfhydryl protected glutathione prodrugs were known in the art (see figure 2 of the present application and D1-D5). D1 discloses a process for the preparation of glutathione S-acyl derivatives and suggests their use as glutathione prodrugs (see column 1, line 24-32). Treatment of diseases associated with oxidative stress in a cell by using compounds increasing the gluthathione levels in a cell (glutathione prodrugs) was well known in the art (see documents D6-14). The skilled person would have combined the teachings of D1 with any of the disclosures of document D6-14, without the exercise of inventive skill and with a reasonable expectation of success in order to solve the problem posed (also knowing from eg. D15 effective protection against hepatoxicity with other sulfhydryl protected thiol prodrugs such as L-CySSME).

In view of the cited documents the subject-matter of the present application appears not involve an inventive step in the sense of Art. 33(3) PCT.

3 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

3.1 Claims 58-62,67-71,76-80,85-89,94,95 fulfil the requirements of (Art. 33(4) PCT)

3.2 For the assessment of the present claims 1-10,20-39,46-51,57 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.